The balancing brain

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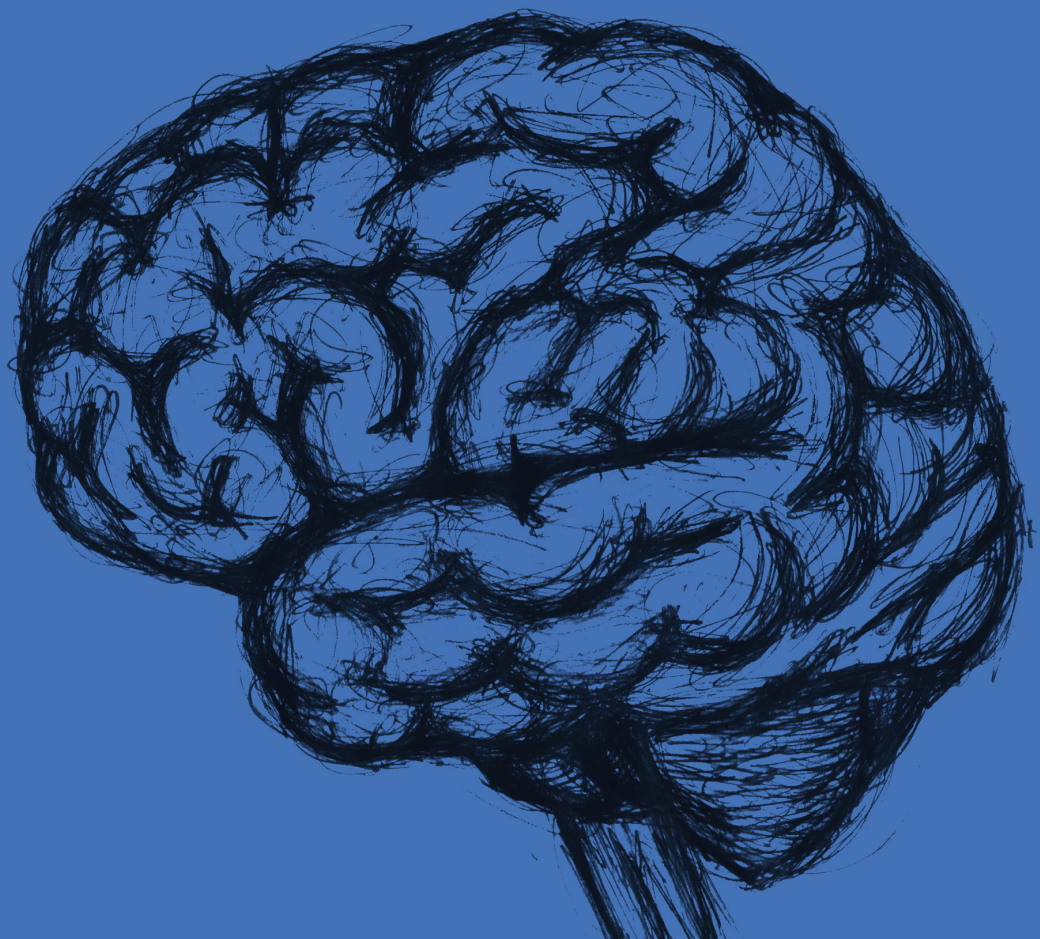
CHAPTER 1

General Introduction



CHAPTER 1

GENERAL INTRODUCTION

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MULTIPLE SCLEROSIS IN NUMBERS & CLINICAL COURSE

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disorder of the central nervous system (CNS). According to the World Health Organization (WHO), MS is one of the most common causes of neurological disability in young adults. More than two million people worldwide suffer from MS with a higher incidence in women than in men, with ratios as high as 3:1.[1] The disease can develop during childhood or at later stage in life, but MS mainly affects young people with a mean age of onset around 30 years. Although MS can occur throughout all parts of the world, the prevalence of MS varies geographically, ranging from 2 per 100.000 in sub-Saharan Africa to 250 per 100.000 in North America and Europa.[2] In the Netherlands, the total number of patients with MS is estimated at 17.000 and 1.800 people are diagnosed with MS each year.[3,4] Although the exact cause of MS is still largely unknown, several risk factors have been proposed, including genetic factors related to immune function[5] and environmental factors related to the substantial geographical variation, such as vitamin D.[6]

The clinical course of patients with MS is heterogeneous and characterized by a wide variety of neurological symptoms. Common presenting symptoms include visual disturbances, loss of coordination, motor weakness, sensory disturbances, gait disturbances, spasticity and more.[7] Although MS is commonly viewed as a typical motor disease, cognitive deficits are also frequently present in patients with MS and can occur independently of physical disability. In fact, up to 70% of all patients experience some degree of cognitive impairment, which is more frequent in progressive phases than in early phases of the disease.[8–10] Like physical symptoms, cognitive deficits can be highly heterogeneous in nature, although it seems that information processing speed and episodic memory deficits are most prominently affected.[11,12] Cognitive dysfunction can influence the patients' lives considerably, from impairments in daily living to social isolation and unemployment. Furthermore, patients with MS who experience cognitive impairment at disease onset have been reported to have a worse prognosis and/or a more rapid disease progression.[13]

Most patients with MS initially develop a relapsing and remitting type of the disease (RRMS) with recurrent episodes (i.e. relapses) of neurological symptoms, followed by partial or complete recovery. After around ten years, fifty percent of RRMS patients will subsequently develop secondary progressive MS (SPMS). This SPMS phase is characterized by an unremitting progressive worsening of clinical symptoms, leading to a continuous and gradual accumulation of clinical deficits. Approximately 10-15% of all MS patients experience this unremitting progressive worsening of symptoms from the disease onset, which is called primary progressive MS (PPMS).[14]

THE CLASSICAL VIEW OF THE MS BRAIN

Focal inflammatory demyelinating lesions in the white matter are considered as the classical pathological hallmark of MS.[15] Myelin forms a fatty sheath around fibers called axons, long projections that extend from the neuron. The white matter is composed of bundles of myelinated axons, which create a network of nerves allowing the passage of electrical signals from and to grey matter regions in the cortex (i.e. neurons). Since the main function of myelin is to protect and insulate axons to enhance transmission of signals, the destruction of myelin in MS interferes with signal propagation, which in turn contributes to the emergence of clinical symptoms.

These white matter MS lesions can occur throughout the brain, but known predilection sites are periventricular areas and areas with a high venous density.[16] Early stages of RRMS are characterized by periods of strong neuro-inflammatory activity and new lesions are frequent,[17] while the immune response seems to dampen down after the conversion to progressive MS.[18,19]

Detecting and visualizing these white matter lesions in clinic is imperative for diagnostic purposes and has been a prominent focus of research using magnetic resonance imaging (MRI; Box A). With the advancement of MRI acquisition techniques, it has become possible to integrate information

BOX A – FROM MAGNET TO PICTURES

To understand how the brain can be imaged, some basic physics need to be introduced. Protons are little particles that have a positive electrical charge, which is constantly spinning around an axis. A moving electrical charge is also called an electrical current, which induce a magnetic force, or magnetic field. Thus, each proton has its own magnetic field and can be seen as a little magnet. Therefore, these protons mainly align with their south and north poles in the direction of the external field (i.e. parallel to the magnet). This type of alignment needs the least energy and is therefore the preferred state, thus more protons are on the lower energy level (i.e. parallel to the external magnetic field) and only a few out of parallel. As there are more protons aligned parallel to the external field, there is a net magnetic moment aligned with, or longitudinal to, the external magnetic field. The protons do not just only align to the magnetic field lines, but they move around in a certain way (i.e. precession). During this precession, the axis of the spinning circles form a cone shape.

Within a MRI scanner, a short burst of electromagnetic waves can be sent in, which is called a radio frequency (RF) pulse. This RF pulse can disturb the protons by exchanging energy with the protons to change their alignment, and go from a lower (i.e. parallel) to a higher energy level (i.e. not in parallel). Only when the RF pulse and the protons have the same frequency, protons can pick up some energy from the radio wave, a phenomenon called resonance. This results in more protons being out of parallel and thus the longitudinal magnetization decreases. When the RF pulse is switched off, longitudinal magnetization increases again (i.e. relaxation). Due to differences in tissue characteristics, this rate of relaxation differs in each part of the brain and thus sends a slightly different signal back to the receiver coil. Decoding where the signal came from, forms the basis of constructing images of brain structures.

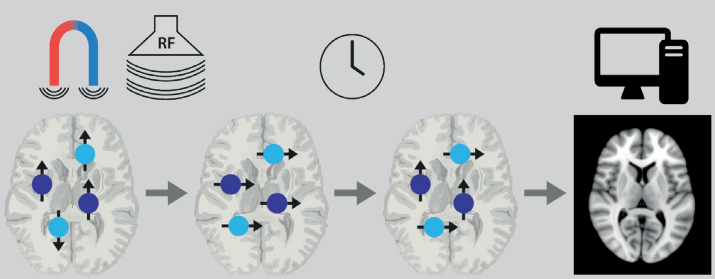

Figure A | From magnet to pictures

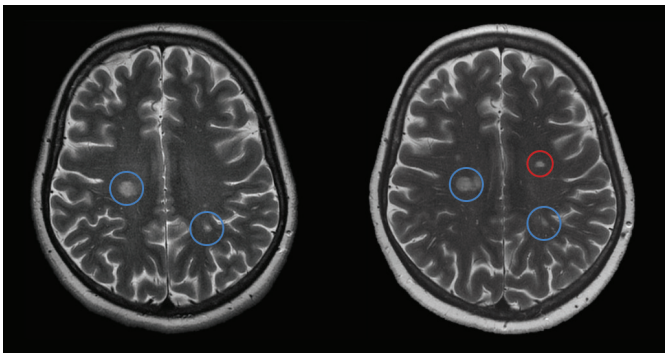

Figure 1 | White matter lesions in MS. Two T2-weighted MRI scans of the same patient at two different time points. T2-weighted scans can be used to visualize lesions in the white matter as areas with hyperintense signal. Some of the white matter lesions (blue circles) are visible at baseline (left) and follow-up (right), but the follow-up MRI scan (right) shows also a lesion (red circle) which was not visible on the baseline scan (i.e. dissemination in time).

from MRI sequences, for example from the so-called T2-weighted images, into sensitive and specific diagnostic criteria, based on the concept of dissemination in time (i.e. attack on more than one occasion) and space (i.e. attack on more than one location in the CNS).[14,20]

FROM PATHOLOGY TO CLINICAL SYMPTOMS

Soon after the emergence of MRI techniques sensitive to detect disseminated white matter lesions (Figure 1), imaging has become a major diagnostic tool for MS. However, attempts to associate the occurrence of focal white matter lesions to clinical measures have revealed a clinico-radiological paradox,[21] showing that the volume and number of white matter lesions only relate relatively poorly with clinical and cognitive functioning.[22,23] The weak relation between white matter lesions and patient functioning have led to the question whether other histopathological processes that are less easily visualized might better explain cognitive and clinical deterioration. Nowadays, several advanced imaging techniques offer opportunities to further quantify such pathological processes, which has improved our understanding of patient functioning.

Although MS has traditionally been considered primarily as a white matter disorder, advanced imaging and histopathological techniques have revealed extensive demyelination in the grey matter as well.[24] Grey matter lesions can already be seen in early stages of the disease,[25,26] accumulate with disease duration and are most prominent in progressive phenotypes.[24] Additionally, grey matter lesions have a much stronger relationship with cognitive dysfunction[27–29] than white matter lesions. In general, grey matter lesions are more frequent and larger in deep invaginations of the brain surface, such as the cingulate gyrus and insular cortex.[16] In the most severe cases, more than 70% of the cortex can be demyelinated.[24] The pathology of grey matter lesions differs from that of white matter lesions in that many of the pathological signatures of white matter lesions, including infiltration of immune cells, complement activation and disruption of the blood-brain barrier, are mostly absent in grey matter lesions.[30,31] Furthermore, grey matter lesions can occur independently of white matter demyelination.[32]

BOX B – MEASURING BRAIN VOLUMES

3D T1-weighted images are most suitable to measure all kind of brain volumes, including whole-brain volume, cortical grey matter volume, deep grey matter volume and white matter volume (Figure B). To extract these volumetric measures, different FSL toolboxes are used. SIENAX performs segmentation of the brain from non-brain tissue and provides whole-brain, grey matter and white matter volume normalized for head size. FIRST can be used to accurately outline the deep grey matter structures, such as the thalamus and hippocampus. The volumes of all deep grey matter structure can be estimated.

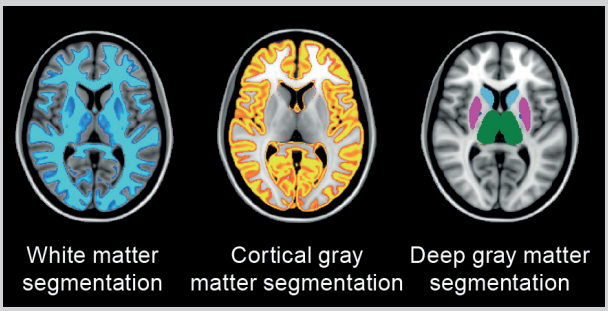

Figure B | To determine the level of atrophy, white matter, gray matter and deep grey matter regions can be segmented, and subsequently the volumes of these segmentations can be computed.

Apart from the focal grey and white matter lesions, neurodegeneration is another important pathological feature of MS. Brain atrophy (Box B) is a commonly used marker of neurodegeneration and explains clinical and cognitive functioning of patients with MS to a larger extent than focal lesions.[33,34] Brain atrophy can occur very early and while white matter atrophy rates appear to remain relatively constant, grey matter atrophy is thought to accelerate after converting to secondary progressive MS. [31,35] Annual whole-brain atrophy rates in the MS population have been reported to be 4 to 8 times higher than in the healthy population, with estimates ranging from 0.4-0.8% of brain tissue loss each year.[35–37] For a long time it was debated what the histopathological substrate of grey matter atrophy in MS could be, but recently it was shown that grey matter atrophy observed on MRI is mainly related to a decrease in neuronal density, neuronal size and axonal density.[38]

MOVING FORWARD - ADVANCED IMAGING TECHNIQUES

Over the last years impressive progress has been made in the development of more advanced imaging techniques to visualize the widespread pathological features of MS. Diffusion tensor imaging, for example, is a technique which allows a researcher to visualize the microstructural organization of the white matter, which cannot be detected with conventional MRI (DTI; Box C). DTI is able to provide rich anatomical information about the white matter and is sensitive to variances in the integrity of this tissue. In patients with MS, DTI has not only revealed reduced integrity in white matter lesions, but also in regions adjacent to white matter lesions, the so-called normal appearing white matter.[39,40] Intriguingly, it turns out that especially damage to

BOX C – DIFFUSION TENSOR IMAGING

Diffusion Tensor Imaging (DTI) is an advanced MRI technique that provides quantitative information about the diffusion of water molecules *in vivo.* DTI measures the direction and the amount of water diffusion. The microstructure of the brain determines the diffusion of water. The movement of water in the white matter preferentially diffuses along the white matter fibers. While in the grey matter the microstructure is less organized and very dense, forcing the water diffusion in many directions. Based on these tissue properties a tensor, or a ellipsoids with a direction, can be computed. In the white matter this ellipsoid shows a high level of directionality, while in the grey matter these ellipsoids are more isotropically (ball) shaped. These tensors can be quantified for each voxel and from these tensors different measures can be computed.

- Axial diffusivity (AD): diffusivity along the axon
- Radial diffusivity (RD): diffusivity perpendicular to the axon
- Mean diffusivity (MD): average diffusion
- Fractional anisotropy (FA): a summary measure that quantifies directionality of diffusion.

Because of the close relation between microstructure and diffusion properties of water, DTI is commonly used to examine the integrity of white matter tissue. Intact white matter (e.g. in the healthy brain) restricts the diffusion of water along the axons, resulting in high directionality of water diffusion. However, when the white matter becomes damaged, such as in MS, diffusion of water is less restricted and can occur in multiple directions, resulting in decreased directionality of water diffusion.

the normal appearing white matter, rather than lesional damage, is correlated to the clinical functioning of patients with MS.[41,42] In addition, cognitively impaired patients displayed more extensive and severe loss of white matter integrity in cognitively relevant white matter tracts compared to cognitively preserved patients with MS, highlighting the value of studying the normal appearing white matter.[41,43]

To examine the impact of disease-related tissue damage on brain function, advanced functional neuroimaging techniques can be used. The structural architecture of the brain is relatively constant over short time ranges, whereas the functional network can be very dynamic over time. Therefore the wide repertoire of flexible functional patterns, upon the more solid structural backbone, is likely to support all kinds of human behavior and gives rise to complex cognitive functions.[44] Within the functional neuroimaging field, brain function can be investigated either during the performance of certain tasks (i.e. task-related fMRI) or in a so-called rest condition (i.e. resting-state fMRI). A commonly used task-related fMRI study design features a chosen paradigm that alternates between periods of performing a particular task and a control state, such as performing a memory task. The two different states are then contrasted to identify brain regions associated with this task, and activation levels are then compared between groups. In MS, two typical phenomena are commonly seen during a task: 1) increased activation of regions also activated in healthy subjects in response to the task and 2) activation of additional areas that are not recruited in healthy subjects.[45–47] Apart from the mapping of regional brain activity,

BOX D – FUNCTIONAL MRI

The fMRI sequence is based on the so-called Blood Oxygenation Level Dependent (BOLD) response. When a brain area is more active, it needs more oxygen and the blood flow increases to this area. Oxygen is delivered to neurons by hemoglobin in capillary red blood cells. Hemoglobin has different magnetic properties in its oxygenated and deoxygenated forms. Hemoglobin without bound oxygen molecules, deoxyhemoglobin, is paramagnetic, while oxygen-bound hemoglobin, oxyhemoglobin is diamagnetic. The various magnetic properties of hemoglobin leads to magnetic signal variation which can be detected using a MRI scanner.

Based on the fMRI sequence, we can analyze brain function by either examining functional activation or functional connectivity. In this thesis, the focus will be on the latter. Functional connectivity is defined as the temporal dependence of activity patterns of anatomically separated brain regions, and is thus inferred on the basis of correlations among measurements of neuronal activity. These patterns of correlated activity in the human brain reflect functional communication between neuronal populations. The level of functional connectivity is typically mapped during a "resting-state", and are therefore not influenced by task performance. Subjects are usually instructed to lay in the scanner with their eyes closed and not to think of anything in particular.

it is also possible to measure how well brain regions are connected to each other, i.e. how strongly they are communicating (Box D). This functional connectivity between regions is often assessed during rest. Resting-state fMRI studies have taught us that the connectivity between brain regions is disturbed in patients with MS, which is associated with cognitive and clinical dysfunction.[48–50]

To summarize, while conventional structural imaging modalities have revealed the typical MS lesions, especially used to diagnose and monitor the disease, more subtle measures of atrophy and normal-appearing brain tissue changes relate more closely with patient functioning. Newer studies have identified the impact of these types of damage using functional imaging modalities, which have disclosed how the brain responds to damage. However, since the brain is a complex system consisting of regions that are either directly or indirectly connected to each other, all these local structural and functional changes are likely to affect regions elsewhere in the brain.

To better understand cognitive and clinical functioning of patients with MS, there is now growing consensus about the need to move from studies focusing on particular single regions to investigate the brain in its entity.[51,52] Investigating the brain as a network endorses the possibility to investigate the brain as a complex system.

THE BRAIN AS A NETWORK

In the latter half of the 19th century the concepts of brain networks emerged with the advent of the "disconnection syndrome" hypothesis propounded by Wernicke, Lichtheim, Liepman, Dejerine and others.[53] This hypothesis was based on neuroanatomical research showing that the brain

was neither uniform nor composed of identical modules, but rather a heterogeneous mosaic of interconnected regions. Therefore this concept can be seen as the precursor of network models as we know it today and as the first biologically plausible account of mental phenomena, based on neuroanatomy and empirical clinical observations rather than philosophy. Nevertheless, this hypothesis competed with many other theories of brain organization in the mid-20th century and lost ground. The concept of a brain network organized to efficiently integrate information was reintroduced by Norman Geschwind in the 1960s.[54] The emergence of advanced MRI modalities, including diffusion tensor imaging (DTI; Box C) and resting-state functional MRI (rs-fMRI; Box D), together with new computational approaches to network analysis, have taught us a lot about the architecture of the brain. Building on the well-established mathematical framework of graph theory developed in computer science, the brain network can be described as a graph (Figure 2) with nodes representing neural elements and edges their structural or functional relations.[55] Without exception, network studies conducted across neural data sets from a variety of species have revealed characteristic non-random features, including high clustering, short path length, as well as modules and highly central hub nodes. It is thought that these patterns of brain-organization are of high functional importance since they facilitate an optimal integration and segregation of information flows. Nowadays, we know that the brain network organization is changed in MS and other neurological disorders[51] and to better understand patient functioning graph based analysis is applied to examine the influence of pathology on the communication between regions on the network level.

THE EARLY DAYS OF FUNCTIONAL CONNECTIVITY STUDIES IN MS

Early functional connectivity studies found increased connectivity in clinically isolated syndrome (CIS) patients[56] and decreased connectivity in progressive MS, which was related to cognitive impairment.[49] Together with task-related fMRI findings of hyperactivation of task-involved regions and recruitment of additional brain regions,[46,57,58] all these increases in brain function (i.e. activity and connectivity) together were interpreted as a compensatory mechanism to sustain clinical and cognitive functions. These findings led to the functional reorganization hypothesis, which asserted that increasing structural damage, in combination with an optimum curve of functional reorganization, results in a delayed development of cognitive dysfunction.[59] Based on this hypothesis, it was proposed that an increase in brain function, both in terms of activity and connectivity, reflects a functional reorganization mechanism which compensates for accumulating structural damage, resulting in maintaining cognitive dysfunction. However, at that point in time, the functional connectivity field was still in its infancy, and the conclusion of compensation was purely based on the direction of the effect, i.e. increases were seen as good, and decreases as bad. Soon after this hypothesis was coined, the field expanded enormously with findings that did not fit the previously stated functional reorganization hypothesis, and showed this model to be incomplete and overly simplistic. [60] Nevertheless, these studies have taught us that the observed changes in the level of functional connectivity are able to discriminate cognitive and MS phenotypes. Since the efficiency of a network strongly depends on the topological organization of a brain network, it is likely that changes in functional connectivity, either increases or decreases, which influence the functional network topology, reduce the global network efficiency.[60] In the healthy brain, the functional network is constructed in a cost-

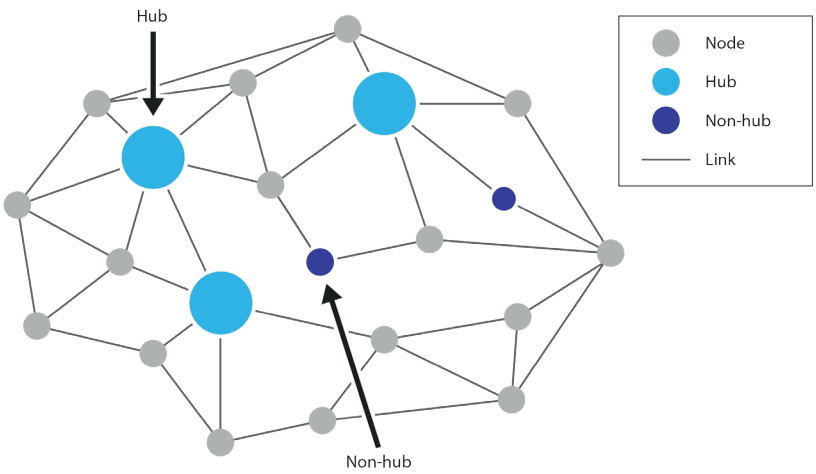

Figure 2 | Graphical representation of the brain. Network measures are shown in a graph with nodes (grey dots) and edges (grey lines). Some of the nodes are characterized by a high level of clustering (red) and others by a low level of clustering (blue). The distance between two nodes is referred to as the path length (green dotted line).

efficient way characterized by both scale-free and small-world properties, which make efficient information flow throughout the brain feasible.[61,62] In short, this means that brain regions are not randomly or evenly connected, and that most brain regions are not neighbours of one another, but can be reached in a small number of steps. There is now growing consensus that optimal brain functioning requires regional specialization with efficient global information transfer and integration.[63] A wide variety of topological characteristics among brain regions are necessary to support both processes of information integration and segregation.

ADVANCES IN THE FUNCTIONAL NETWORK FIELD

The reason why some studies mainly identified increases and others mainly decreases in functional connectivity remains unclear and could be numerous, including different patient groups, a variety of methodological approaches and changes could be region specific. In addition, the observed high between-subject variability of the functional network in both patients and controls makes it even more complicated.[64] Despite that the composition and strength of individual functional networks varies considerably between individuals, functional MRI studies typically collapse data from many subjects in order to draw interferences about differences in fMRI connectivity patterns between groups.[65] To become more sensitive to specific topological changes and to enhance the between-subject comparability, it is necessary to consider the variability of these individual network properties when comparing functional networks across groups. This provides the possibility to investigate which connections are the strongest and which are the weakest within an individual functional network and could provide insight in the underlying functional scaffold. In this thesis, we aim to investigate changes in the functional network of patients

with MS, while taking the individual scaling of connectivity levels within the brain network into account. This measure would then allow for a more sensitive investigation of changes in the functional network topology, by looking at connectivity shifts between different parts of the brain network. In other words, it provides the possibility to investigate shifts in the network balance, which connections become stronger or weaker in relation to clinical deficits.

As a small change in the make-up of the functional scaffold is likely to change the optimal efficiency, we expected that these changes are closely related to clinical functions. Furthermore, we expected that changes in the functional network are not random but follow certain patterns instead. For example, it could be that functional connectivity changes follow the apparent pattern of atrophy, from deep grey matter structures to cortical regions. Eventually, the accumulating structural damage and the resulting pressure on the functional network may lead to a functional "network collapse", i.e. a sudden drop in efficiency. Furthermore, we expected that some functional changes have more severe network (and clinical) consequences than others. For example, changes in regions that are highly connected, the so-called hub regions, which are highly responsible for the network efficiency. This high grade of efficiency can be achieved via long-distance connections of these hubs to other brain regions and their strong interconnectedness to each other, forming the so-called rich club.[66] Their topological centrality and embedding within the network support efficient processing of signals throughout the brain making them functionally valuable and relevant. In neurological disorders like MS, it could be that clinical and cognitive dysfunction can be related to disturbances of hub regions[67,68]

STRUCTURAL NETWORKS – MIND THE GAP

Apart from constituting functional networks based on resting-state fMRI data, it is also possible to map structural networks. However, there is less known about the impact of MS pathology on the structural network, partly due to methodological challenges of current algorithms that are used to map white matter tracts in the healthy brain and across neurodegenerative diseases. In MS, these tracing algorithms are hampered by the presence of focal white matter lesions making it complicated to map the white matter tracts.[69,70] For this reason, most of the MS studies that have addressed the quality of the white matter tracts have applied Tract Bases Spatial Statistics (TBSS),[71] which allows to investigate voxel-based changes in whole brain white matter integrity. Although studies have observed loss of white matter integrity throughout the brain, it is not known whether loss of white matter integrity occurs randomly throughout the brain or whether there are patterns to the white matter damage, nor whether these patterns could be clinically relevant. If we assume that individual white matter tracts are not isolated but are embedded within a network of white matter tracts and thus connected to each other, it would be likely that changes anywhere in the white matter leads to changes in other, most likely connected, white matter tracts as well. To mimic a network-based approach that allows us to examine white matter changes in relation to each other, it could be investigated whether patterns in white matter integrity loss occur. Eventually, it would be of interest to investigate structural networks in MS. Nowadays, alternative methods, such as correlating measures of cortical thickness, have been used to map the structural network in patients with MS.[70,72] These studies have shown that especially the extent of white matter lesions seem to proportionally disrupt the efficiency of the structural network.[72] To be able to apply tractography algorithms to perform structural network

analyses in MS studies, consensus on how to estimate the best possible structural network is first needed. In this thesis, different methodological choices that have to be made along the construction of structural networks are evaluated and recommendation for future studies are provided.

FUNCTIONAL VERSUS STRUCTURAL CHANGES

The two paragraphs before describe the state of the art of the functional and structural MRI field in MS separately. However, when we engage a certain task, the brains' functional and structural architecture together enable efficient processing of information across different brain regions which give rise to complex behavior, including cognitive functions.[44,73] However, the exact interaction between the functional and structural connectivity is far from simple. Mapping the interplay between functional and structural brain could potentially better explain complex behavior than studying one or the other, especially because previous studies have suggested that there is no simple one-to-one relation between structural and functional properties of the brain. Functional connections are observed between two brain regions without a direct structural link, indicating that these regions can only reach each other through indirect structural pathways. Despite previous imaging studies have taught us that both functional and structural measures could be affected in MS,[45,48,74,75] studies integrating functional and structural measures are missing. Although structural and functional brain characteristics are intertwined to a certain extent, structural damage can occur in the presence of minor functional changes, but may also involve severe functional changes.[76] This emphasizes the necessity to investigate both in relation to each other. Without structural measures, information about the integrity and quality of the structural brain architecture is missing. In absence of functional measures, we most likely miss information regarding the functionality of the structural brain architecture. Until now, it is unclear whether different severities of functional and structural damage are associated with different clinical and/or cognitive phenotypes. In the MS field, a first step could be to individually map the level of structural and functional changes, and investigate whether a disparity in the level of structural and functional exist in patients with MS.

AIM OF THIS THESIS

The general aim of the studies presented in this thesis is to expand our understanding of MS as a network disease by deciphering patterns in structural and functional brain changes in relation to the clinical picture of MS. To achieve this, we used advanced multi-model MRI techniques and both existing as well as innovative analyzing methods. This thesis is divided into three different chapters each covering a more specific research question while supporting the general aim:

1. Which shifts in the functional network balance can we observe in MS and what is the clinical relevance of these shifts?

2. Can we provide a better explanation of the clinical picture of MS using advanced diffusion tensor imaging at a voxel- and network-based level, and which are the best methodological approaches to map structural networks?

3. What is the interplay between functional and structural brain changes, and would studying the brain by combining both measures help to understand cognitive function better than studying either in isolation?

In **CHAPTER 2** functional network shifts are not only investigated in relation with cognitive deficits, but also in relation with different phases of MS and treatment. The role of advanced DTI methods is addressed in **CHAPTER 3**. In this chapter, we not only investigate voxel-based changes in WM integrity and their cognitive relevance in SPMS, but also whether we can detect non-random patterns of damage in the WM. Finally, different methodological approaches to map structural networks are compared and evaluated. After studying functional and structural changes separately, in **CHAPTER 4** we investigate the interplay between structural and functional changes in order to understand the mechanism underlying cognitive deficits better, for example by studying groups of patients with severe structural damage but few functional changes, and vice versa. In **CHAPTER 5** the findings of the performed studies are summarized, integrated and discussed.

REFERENCES

1. Kingwell E, Marriott JJ, Jetté N, et al. Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC Neurol. 2013;13:128.
2. Multiple Sclerosis International Federation, Atlas of MS 2013: mapping multiple sclerosis around the world, Multiple Sclerosis International Federation, London (2013).
3. Gommer AM, Poos MJJC. Cijfers multiple sclerose (prevalentie, incidentie en sterfte) uit de VTV 2010. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM.
4. Uitdehaag BMJ, Kobelt G, Berg J, Capsa D, Dalén D. New insights into the burden and costs of multiple sclerosis in Europe: Results for the Netherlands. Mult Scler J. 2017;23:117-129.
5. Gourraud PA, Harbo HF, Hauser SL, Baranzini SE. The genetics of multiple sclerosis: An up-to-date review. Immunol Rev. 2012;248:87–103.
6. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: The role of infection. Ann. Neurol. 2007;61:288–299.
7. Compston A, Coles A. Multiple sclerosis. Lancet 2008;25:1502–1517.
8. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. Lancet 2008;7:1139–1151.
9. Amato MP, Portaccio E, Goretti B, et al. The Rao ' s Brief Repeatable Battery and Stroop test: normative values with age, education and gender corrections in an Italian population. Mult Scler J. 2006;12:787–793.
10. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685–691.
11. Benedict RHB, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol. 2002;16:381–397.
12. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Int Neuropsychol Soc. 2006;12:549–558.
13. Bergamaschi R. Prognostic Factors in Multiple Sclerosis. Int. Rev. Neurobiol. 2007; 79:423–447.
14. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014;83:278–286.
15. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol. 2015;15:545–558.
16. Haider L, Zrzavy T, Hametner S, et al. The topograpy of demyelination and neurodegeneration in the multiple sclerosis brain. Brain 2016;139:807–815.
17. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009;132:1175–1189.
18. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14:183–193.
19. Lassmann H. Pathology and disease mechanisms in different stages of multiple sclerosis. J Neurol Sci. 2013;333:1–4.
20. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016;15:292–303.
21. Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. Curr Opin Neurol. 2002;15:239–245.
22. Rovaris M, Comi G, Filippi M. MRI markers of destructive pathology in multiple sclerosis-related cognitive dysfunction. J Neurol Sci. 2006;245:111–116.
23. Benedict RHB, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. Arch Neurol. 2004;61:226–230.

24. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005;128:2705–2712.

25. Lucchinetti CFC, Popescu BFGB, Bunyan RF, et al. Inflammatory Cortical Demyelination in Early Multiple Sclerosis. N Engl J Med. 2011;365:2188–2197.

26. Haider L, Simeonidou C, Steinberger G, et al. Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. J Neurol Neurosurg Psychiatry. 2014;85:1386–1395.

27. Mike a, Glanz BI, Hildenbrand P, et al. Identification and clinical impact of multiple sclerosis cortical lesions as assessed by routine 3T MR imaging. AJNR. Am. J. Neuroradiol. 2011;32:515–521.

28. Roosendaal SD, Moraal B, Pouwels PJ, et al. Accumulation of cortical lesions in MS: relation with cognitive impairment. Mult Scler. 2009;15:708–714.

29. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol. 2009;66:1144–1150.

30. Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. Lancet Neurol. 2008;7:841–851.

31. Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis. Curr Opin Neurol. 2014;27:271–278.

32. Bö L, Geurts JJG, van der Valk P, Polman C, Barkhof F. Lack of correlation between cortical demyelination and white matter pathologic changes in multiple sclerosis. Arch Neurol. 2007;64:76-80.

33. Zivadinov R. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2001;70:773–780.

34. Fisniku LK, Chard DT, Jackson JS, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol. 2008;64:247–254.

35. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: A longitudinal study. Ann Neurol. 2008;64:255–265.

36. Miller DH, Barkhof F, Frank JA, Parker GJM, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Brain 2002;125:1676–1695.

37. De Stefano N, Giorgio A, Battaglini M, et al. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. Neurology 2010;74:1868–1876.

38. Popescu V, Klaver R, Voorn P, et al. What drives MRI-measured cortical atrophy in multiple sclerosis? Mult Scler. 2015;21:1280–1290.

39. Kealey SM, Kim Y, Whiting WL, Madden DJ, Provenzale JM. Determination of multiple sclerosis plaque size with diffusion-tensor MR Imaging: comparison study with healthy volunteers. Radiology. 2005;236:615–620.

40. Vrenken H, Geurts JJG, Knol DL, et al. Normal-appearing white matter changes vary with distance to lesions in multiple sclerosis. Am J Neuroradiol. 2006;27:2005–2011.

41. Hulst HE, Steenwijk MD, Versteeg A, et al. Cognitive impairment in MS: Impact of white matter integrity, gray matter volume, and lesions. Neurology. 2013;80:1025–1032.

42. Roosendaal SD, Geurts JJG, Vrenken H, et al. Regional DTI differences in multiple sclerosis patients. Neuroimage 2009;44:1397–1403.

43. Francis PL, Chia TL, Jakubovic R, et al. Extensive White Matter Dysfunction in Cognitively Impaired Patients with Secondary-Progressive Multiple Sclerosis. AJNR Am J Neuroradiol. 2014;35:1910-1915.

44. Park H-J, Friston K. Structural and Functional Brain Networks: From Connections to Cognition. Science 2013;342:1238411–1238411.

45. Hulst HE, Schoonheim MM, Roosendaal SD, et al. Functional adaptive changes within the hippocampal memory system of patients with multiple sclerosis. Hum Brain Mapp. 2012;33:2268–2280.

46. Staffen W, Mair A, Zauner H, et al. Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. Brain 2002;125:1275–1282.

47. Rocca MA, Valsasina P, Hulst HE, et al. Functional correlates of cognitive dysfunction in multiple sclerosis: A multicenter fMRI Study. Hum Brain Mapp. 2014;35:5799-5814

48. Hawellek DJ, Hipp JF, Lewis CM, Corbetta M, Engel AK. Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. Proc Natl Acad Sci U S A. 2011;108:19066–19071.

49. Rocca MA, Valsasina P, Absinta M, et al. Default-mode network dysfunction and cognitive impairment in progressive MS. Neurology 2010;74:1252–1259.

50. Schoonheim MM, Hulst HE, Brandt R, et al. Thalamus structure and function determines severity of cognitive impairment in multiple sclerosis. Neurology 2015;84:776–783.

51. Stam CJ. Modern network science of neurological disorders. Nat Rev Neurosci. 2014;15:683–695.

52. Sporns O. The human connectome: a complex network. Ann N Y Acad Sci. 2011;1224:109–125.

53. Catani M, Mesulam M. What is a disconnection syndrome? Cortex 2008;44:911–913.

54. Geschwind N. Disconnexion syndromes in animals and man. Brain 1965;88:237–294.

55. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC. Organization, development and function of complex brain networks. Trends Cogn Sci. 2004;8:418–425.

56. Roosendaal SD, Schoonheim MM, Hulst HE, et al. Resting state networks change in clinically isolated syndrome. Brain 2010;133:1612–1621.

57. Reddy H, Narayanan S, Arnoutelis R, et al. Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 2000;123:2314–2320.

58. Mainero C, Caramia F, Pozzilli C, et al. fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. Neuroimage 2004;21:858–867.

59. Schoonheim MM, Geurts JJG, Barkhof F. The limits of functional reorganization in multiple sclerosis. Neurology 2010;74:1246–1247.

60. Schoonheim MM, Meijer KA, Geurts JJG. Network collapse and cognitive impairment in multiple sclerosis. Front Neurol. 2015;6:82.

61. Bullmore E, Sporns O. The economy of brain network organization. Nat Rev Neurosci. 2012;13:336–349.

62. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature 1998;393:440–442.

63. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 2009;10:186–198.

64. Chou YH, Panych LP, Dickey CC, Petrella JR, Chen NK. Investigation of long-term reproducibility of intrinsic connectivity network mapping: A resting-state fMRI study. Am J Neuroradiol. 2012;33:833–838.

65. Finn ES, Shen X, Scheinost D, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat Neurosci. 2015;18:1–11.

66. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J Neurosci. 2011;31:15775–15786.

67. Tomasi D, Volkow ND. Functional connectivity hubs in the human brain. Neuroimage 2011;57:908–917.

68. van den Heuvel MP, Sporns O. Network hubs in the human brain. Trends Cogn Sci. 2013;17:683–696.

69. Daams M, Steenwijk MD, Wattjes MP, et al. Unraveling the neuroimaging predictors for motor dysfunction in long-standing multiple sclerosis. Neurology 2015;85:248–255.

70. Steenwijk MD, Daams M, Pouwels PJW, et al. Unraveling the relationship between regional gray matter atrophy and pathology in connected white matter tracts in long-standing multiple sclerosis. Hum Brain Mapp. 2015;36:1796–1807.

71. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis

of multi-subject diffusion data. Neuroimage 2006;31:1487–1505.

72. He Y, Dagher A, Chen Z, et al. Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load. Brain 2009;132:3366–3379.

73. Buckner RL, Bandettini PA, O'Craven KM, et al. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci U S A. 1996;93:14878–14883.

74. Schoonheim MM, Popescu V, Rueda Lopes FC, et al. Subcortical atrophy and cognition: sex effects in multiple sclerosis. Neurology 2012;79:1754–1761.

75. Dineen RA, Vilisaar J, Hlinka J, et al. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain 2009;132:239–249.

76. Hillary FG, Grafman JH. Injured Brains and Adaptive Networks: The Benefits and Costs of Hyperconnectivity. Trends Cogn Sci. 2017;21:385–401.